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Regioselective Asymmetric α,α-Bisalkylation of Ketones via Complex-Induced *Syn*-Deprotonation of Chiral *N*-Amino Cyclic Carbamate Hydrazones

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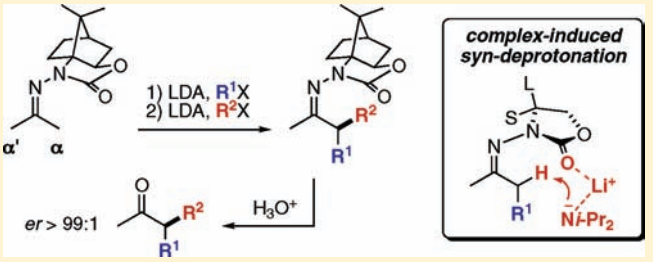
Supporting Information

ABSTRACT: The first general method for the asymmetric α,α-bisalkylation of ketones having both α- and α′-protons is described. Both excellent regio- and stereoselectivity result. The transformation is enabled by complex-induced *syn*-deprotonation (CIS-D), which completely reverses the inherent preference of lithium diisopropylamide (LDA) to remove the less sterically hindered of two similarly acidic protons. CIS-D also overrides the normal tendency of LDA to remove the more strongly acidic proton in a substrate having protons differing significantly in their acidity. The regiochemical outcome is, thus, the opposite of that normally obtained for kinetic LDA-mediated deprotonation of ketones and (*S*)-1-amino-2-methoxymethylpyrrolidine/(*R*)-1-amino-2-methoxymethylpyrrolidine (SAMP/RAMP)hydrazones. Conveniently, this strategy allows access to either ketone enantiomer using a single enantiomer of the auxiliary. The utility of this method is demonstrated by a concise and highly efficient formal synthesis of both (*R*)- and (*S*)-stigmolone.



INTRODUCTION

The asymmetric α-alkylation of ketones is an important yet highly challenging transformation.[1] Indeed, with regard to the latter assertion, in contrast to the α-alkylation of carboxylic acid derivatives, for which numerous chiral auxiliary-based asymmetric methods are available,[2] only a single method is available for ketone α-alkylation that has found application in the synthesis of natural products, albeit in only a handful of cases.[1c] This method employs the well-known Enders (*S*)-1-amino-2-methoxymethylpyrrolidine/(*R*)-1-amino-2-methoxymethylpyrrolidine (SAMP/RAMP) chiral auxiliaries.[1a−c] As in situations involving chiral carboxylic acid derivatives,[2] both azaenolate geometry and facial selectivity must be controlled during the alkylation of hydrazones. However, adding to the complexity of hydrazone alkylation is the need for tight regiochemical control during deprotonation of nonsymmetrical ketone derivatives having both α- and α′-protons (cf. **2**, Scheme 1a). For SAMP/RAMP hydrazones this is achieved kinetically using lithium diisopropylamide (LDA) and generally results in removal of the more sterically accessible proton.[1a−c,3] As a result, the controlled asymmetric α,α-bisalkylation of ketone derivatives having indistinguishable α- and α′-protons is not possible (cf. **2** → **3** + **4**). However, if such a transformation could be achieved, then, given the expansive body of literature on ketone manipulation, the bisalkylated products[4] would provide access to an unusually wide array of chiral, nonracemic intermediates for use in asymmetric synthesis. In what follows, we describe our studies on the first method for the asymmetric α,α-bisalkylation of ketones having both α- and α′-protons (cf. **7** → **8** → **9** → **5**). Regiocontrol is achieved using chiral *N*-amino cyclic carbamate (ACC) hydrazones through a process we term complex-induced *syn*-deprotonation (CIS-D) (Scheme 2b). This bisalkylation method is remarkable in producing nearly perfect levels of *both* stereo- and regioselectivity. Moreover, the regiochemical outcome is the opposite of that normally obtained for kinetic LDA-mediated deprotonation of ketones and SAMP/RAMP hydrazones. Conveniently, this strategy allows access to either ketone enantiomer using a single enantiomer of the auxiliary by simply altering the alkylation sequence. To highlight the effectiveness and efficiency of this α,α-bisalkylation method, a formal asymmetric synthesis of both (*R*)- and (*S*)-stigmolone was carried out.

We recently described the development of ACC auxiliaries for asymmetric ketone alkylation.[5−8] In contrast to other methods, the auxiliaries are both easily introduced into and removed from ketones, with nearly quantitative recovery. Furthermore, deprotonation is rapid, and alkylation does not require extremely low temperature, yet it proceeds with excellent stereoselectivity and substantially greater yields. A key design feature of these auxiliaries was the placement of a carbonyl group adjacent to the hydrazone moiety for enhanced α-proton acidity and tight chelation at the level of the azaenolate.[5] The carbonyl was also intended to influence the regiochemistry of deprotonation to

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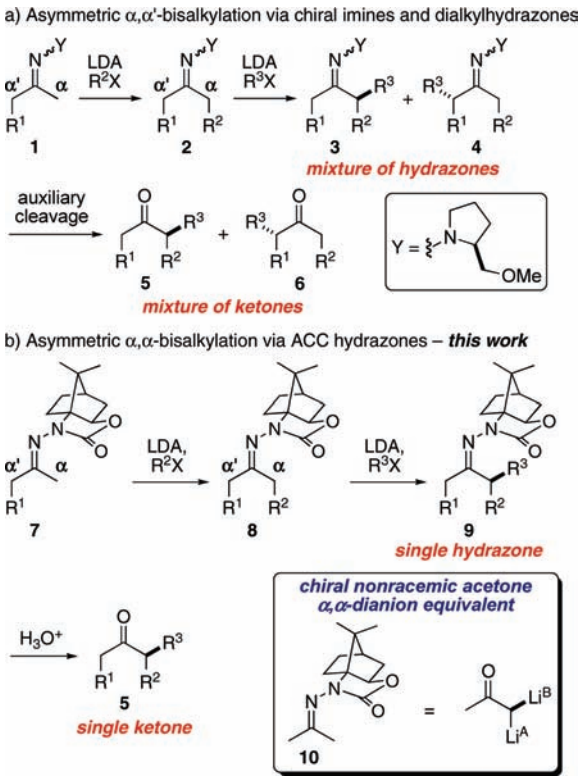
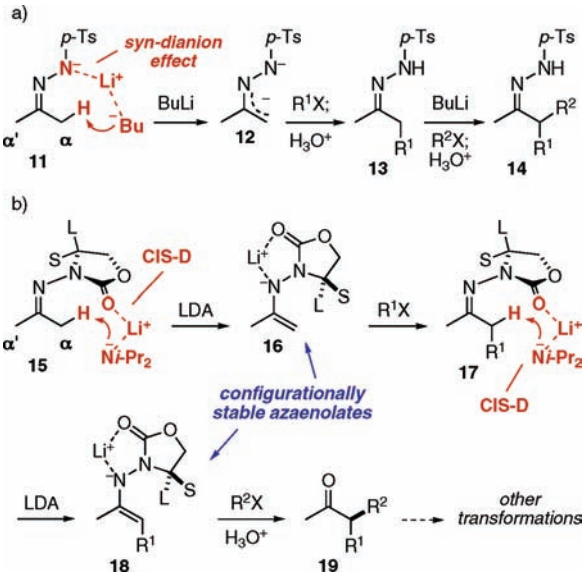
Scheme 1. Regioselectivity of Bisalkylation of (a) Chiral Dialkyl Hydrazones Compared to (b) ACC Hydrazones



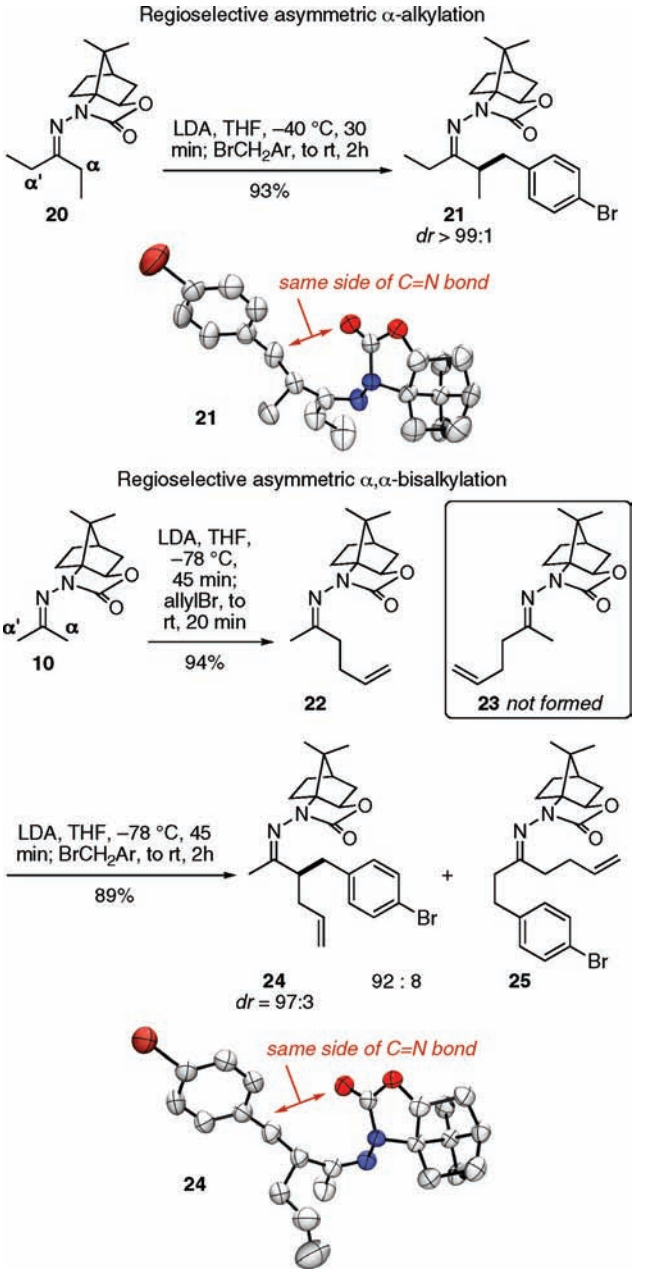
Scheme 2. (a) *Syn*-Dianion Effect in Sulfonyl Hydrazones and (b) α,α-Bisalkylation via Complex-Induced *Syn*-Deprotonation (CIS-D) of ACC Hydrazones[a]



[a] S = small substituent; L = large substituent.

enable the α,α-bisalkylation of ketones having both α- and α′-protons. Our inspiration for this was the *syn*-dianion effect of *N*-sulfonyl hydrazones.[9] In the *syn*-dianion effect (Scheme 2a), an *N*-centered monoanion (**11**) obtained from deprotonation of a

Scheme 3. Studies on Complex-Induced *Syn*-Deprotonation



sulfonyl hydrazone directs an incoming base to remove a proton on the same side of the C═N bond that it is on. This results in the formation of a configurationally stable dianion that can be alkylated (**12** → **13**). The process may then be repeated (**13** → **14**), again in a configurationally controlled manner with regard to the hydrazone C═N bond geometry. We reasoned that a similar directed deprotonation might be possible by simply utilizing the carbonyl lone pair[10] of an ACC hydrazone via CIS-D. Here, the carbonyl oxygen electrons would coordinate with the base, directing deprotonation to the same side of the carbon−nitrogen double bond (cf. **15** → **16**, **17** → **18**). If such a directed deprotonation could be achieved, then providing that the azaenolates involved (cf. **16**, **18**) were configurationally stable and that the monoalkylation product (cf. **17**) did not isomerize once formed, asymmetric α,α,-bisalkylation would be possible.[11]

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RESULTS AND DISCUSSION

Given the novelty of the proposed transformation, at the outset of our studies we did not know if the intended CIS-D would occur, or, if it did, whether the resulting azaenolate intermediates (**16**, **18**) would be configurationally stable about the original carbon−nitrogen double bond. This would be essential for the proposed asymmetric α,α-bisalkylation process for two reasons. First, since the monoalkylated hydrazone (**17**, Scheme 2) would have to undergo a second directed deprotonation for regiocontrolled access to the second azaenolate (**17** → **18**), it would be critical that isomerization of the hydrazone double bond did not occur during the first alkylation (**15** → **17**), so that the auxiliary carbonyl could again direct deprotonation to the α-poistion. Second, since addition of the second electrophile would have to occur in a diastereoselective fashion, the auxiliary would need to be positioned on the same side of the carbon−nitrogen double bond from which the electrophile was approaching to ensure high facial selectivity.[11]

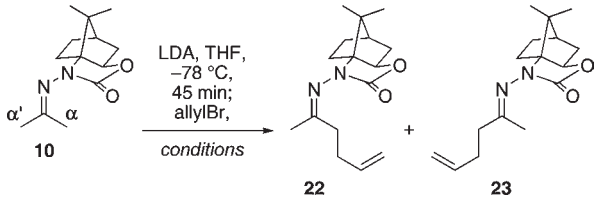
As an initial test of the mechanistic course of this reaction with regard to CIS-D, 3-pentanone-derived ACC hydrazone **20** was prepared and then alkylated with *p*-bromobenzyl bromide (Scheme 3). A single alkylated product was detected by ^{1}H NMR from this reaction and was subsequently analyzed by X-ray crystallography (Scheme 3) and confirmed to be **21**. We were pleased to find that the *p*-bromobenzyl substituent and the auxiliary were positioned on the same side of the hydrazone C═N bond in this compound, supporting the notion of CIS-D. Theoretical studies were also carried out on a simplified model system corresponding to **20** that provided support for intramolecular deprotonation occurring preferentially at the α-position (cf. **15** → **16**) over the α′-position.[6]

With these encouraging results as a basis, we undertook an α, α-bisalkylation sequence starting from acetone-derived hydrazone **10**. To do so, allyl bromide was added to a −78 °C THF solution of the lithium azaenolate derived from **10**. The cold bath was removed immediately following addition, and the mixture was allowed to stir for 20 min and then quenched with H_2O. We were pleased to find that this gave exclusively the α-regioisomer (**22**) in excellent yield. Since the allylation product was not crystalline, its structure was deduced to be **22** by independently preparing a 15:85 mixture of **22** and **23**, respectively, via acid-catalyzed condensation of 5-hexen-2-one and auxiliary **26**.[12] The NMR data of the minor, thermodynamically less favored isomer of this reaction matched the NMR data of the allylation product obtained from **10**, strongly suggesting this compound to be **22**. In the key part of this bisalkylation study, **22** was subjected to a second alkylation reaction using *p*-bromobenzyl bromide as the alkylating agent. As hoped, the major product was indeed the α, α-bisalkylated compound (**24**), which was confirmed by X-ray crystallography (Scheme 3). Once again, alkylation had occurred on the same side of the C═N bond as the auxiliary carbonyl. The diastereoselectivity of the transformation leading to **24** was also excellent (dr = 97:3). To our knowledge, this was the first instance of asymmetric α,α-bisalkylation of a ketone having both α- and α′-protons.

With proof of concept established, we began a further investigation into this new asymmetric alkylation method. Unfortunately, our attempts to prepare more of compound **22** using the procedure describe above resulted in variable yields of product and at times led to the formation of **23** as well, the latter presumably obtained via in situ isomerization of **22**. Thus, in an effort to develop a more reliable protocol for the monoalkylation, we conducted a survey of the reaction conditions, as outlined in Table 1. We eventually found that, by holding the alkylation temperature constant at 4 °C and allowing the reaction to proceed for 1.5 h, an excellent yield of **22** could reliably be produced in a fully regiocontrolled manner (entry 5). Using these conditions, we were able to prepare compound **22** starting with up to 5 g of **10**, without compromising the outcome of the reaction.[12] This does not represent the upper limit of the reaction, but simply the largest scale on which we have conducted it to date.

Next, we tested other ACC auxiliaries (**27**−**29**) for their ability to effect regioselective α-alkylation, in the hopes of providing increased flexibility in our later investigations on the second, asymmetric alkylation step. To do so, acetone-derived hydrazones **30**−**32** were prepared,[12] and each of these

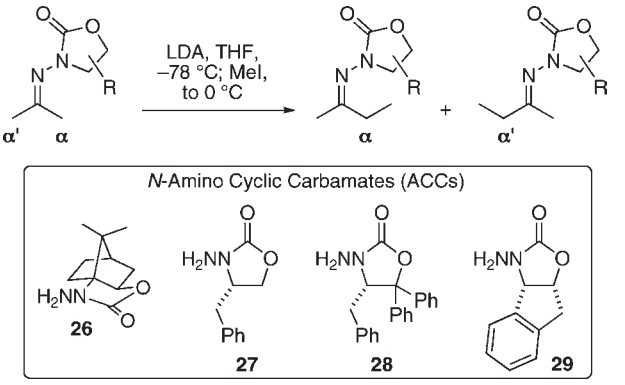
Table 1. Survey of Conditions for the Regioselective Allylation of 10



entry	temp (°C)	time (min)	22:23	yield (%)
1	−78	30	n.d.[a]	<5
2	−20	30	>99:1	70
3	−20	60	>99:1	84
4	4	60	>99:1	93
5	4	90	>99:1	99

[a] Not determined.

Table 2. Regioselective Methylation of ACC Hydrazones 10, 30−32



entry	ACC	acetone hydrazone	methylated hydrazone	α:α′[a]	yield (%)
1	**26**	**10**	**33**	>99:1	96
2	**27**	**30**	**34**	91:9	90
3	**28**	**31**	**35**	98:2	82
4	**29**	**32**	**36**	91:9	93

[a] Determined by HPLC.

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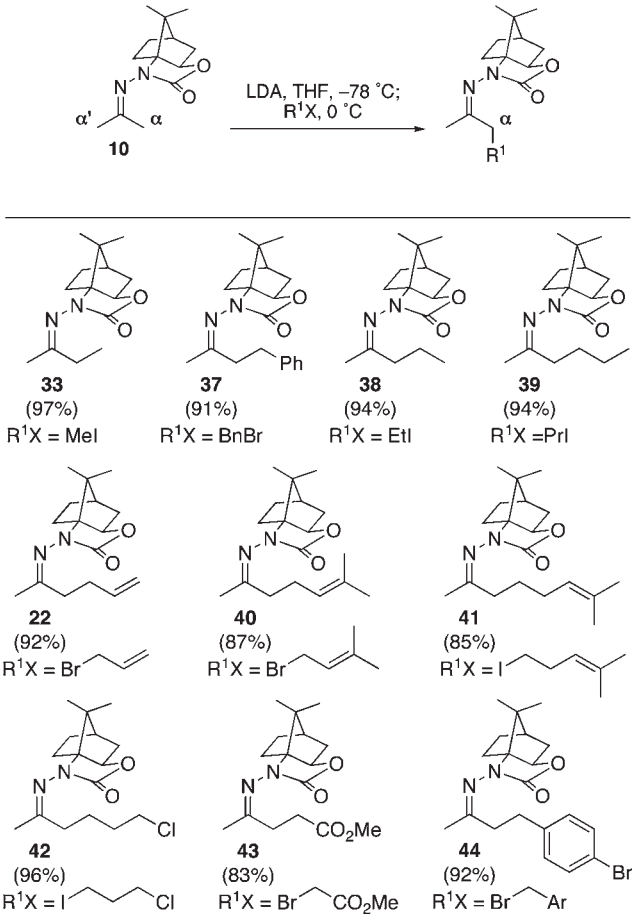
Table 3. Scope and Regioselectivity of the α-Alkylation of 10 via CIS-D



compounds, in addition to **10**, was treated successively with LDA and then MeI using the conditions established above (Table 1, entry 5). As shown in Table 2, under these conditions all four of the hydrazones tested underwent regioselective alkylation strongly favoring formation of the α-product. However, of these, hydrazone **10**, formed from ACC auxiliary **26**, gave the best result, providing a *single* regioisomer (entry 1). Consequently, auxiliary **26** was used for the remainder of our studies.

At this stage, the scope of the monoalkylation was examined using hydrazone **10** and a variety of alkyl halides (Table 3). In each case the alkylation proceeded with excellent yield and gave only the α-regioisomer.[13] The transformations proved highly reliable and were very easy to carry out. These results provided further evidence of CIS-D occurring during azaenolate formation. Moreover, they supported the notion that the azaenolate intermediate was configurationally stable under the reaction conditions and that isomerization of the hydrazone did not occur in situ following alkylation.[14]

With a highly effective regioselective, isomerization-free monoalkylation procedure established, we began a further investigation of the regio- and stereocontrolled incorporation of the second alkyl group at the α-position. This second alkylation requires an even more demanding application of CIS-D than the first, in that the ACC auxiliary in this instance must completely reverse the inherent preference of LDA for removal of the more

Scheme 4. Studies on Regioselective Asymmetric α,α-Bisalkylation

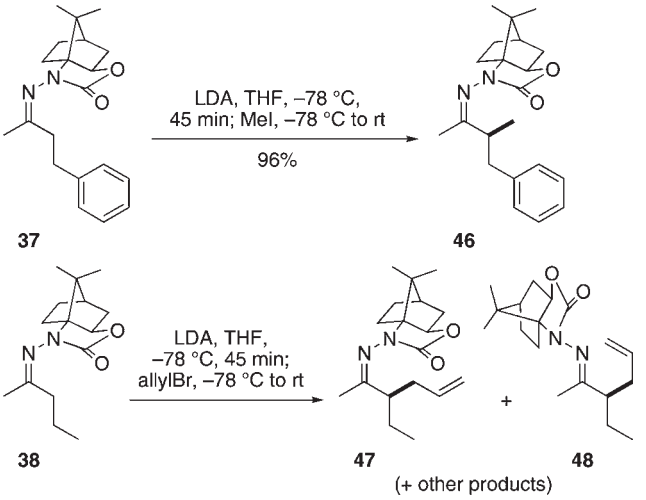
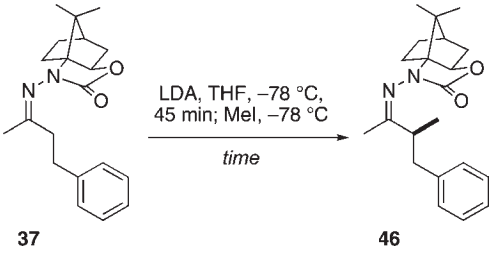


Table 4. Methylation of 37



entry	temp (°C)	time (h)	dr[a]	yield (%)
1	−78	1	n.d.[b]	<5
2	−78	6	n.d.[b]	22
3	−78	12	>99:1	68
4	−78	24	>99:1	98

[a] Determined by HPLC analysis. [b] Not determined.

sterically accessible α′-methyl protons of the monoalkylated compounds (cf. Table 3) and instead direct the removal of the *less accessible* α-methylene protons. Moreover, since a stereogenic center is formed, the auxiliary must also provide high levels of asymmetric induction. While the result of our preliminary test of this transformation described above (**22** → **24**, Scheme 3) was very promising, there was clearly room for improvement with regard to both the regio- and stereochemical outcome.

To investigate the possibility of such improvement, we chose to study the methylation of hydrazone **37** (Scheme 4). We began by using the conditions employed above for the *p*-bromobenzylation of **22** (Scheme 3), which had produced a 92:8 mixture of **24** and **25**, respectively. We were pleased to find that, under these conditions, the methylation of **37** produced only the α,α-bisalkylation product **46**, reproducibly and in excellent yield. Inspired by this result, we next tried the allylation of **38** under the same conditions. Unfortunately, in stark contrast to the methylation of **37**, this reaction was extremely problematic, providing variable yields and mixtures of products that appeared to include the desired product **47**, as well as the undesired (*E*)-isomer **48**.

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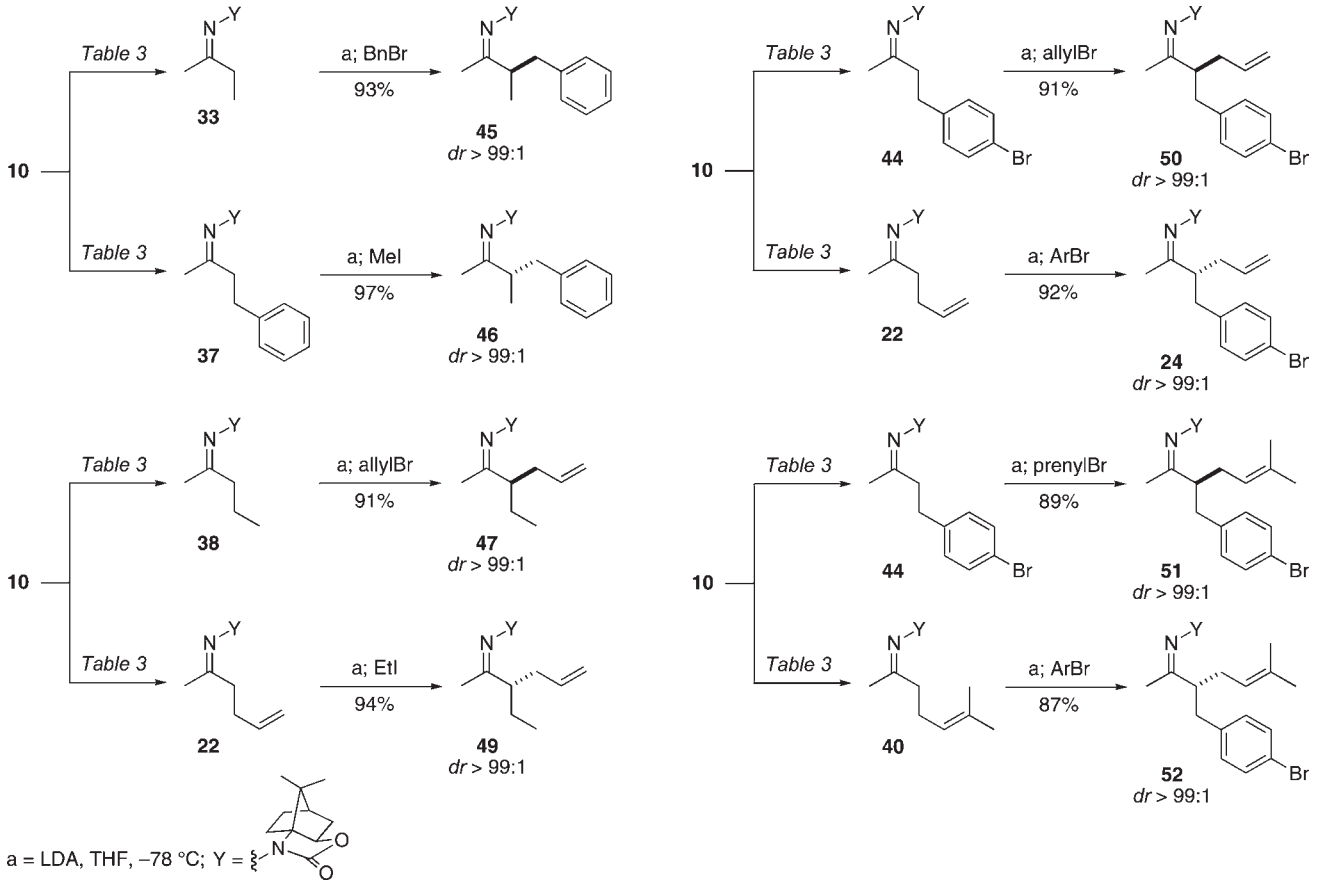
Scheme 5. Regioselective Asymmetric α,α-Bisalkylation



With regard to the formation of **48**, while it was possible that isomerization had occurred subsequent to the allylation, in which case it would have no bearing on the overall level of asymmetric induction (assuming no epimerization occurred during isomerization), we could neither be certain of that nor assume that, if that were the case, the same scenario would apply for other alkylation reactions. We therefore decided to focus on developing conditions that would enable regiocontrolled α,α-bisalkylation without isomerization occurring. We suspected that this might be possible simply by holding the reaction temperature at −78 °C for the entire course of the alkylation, although we were concerned that the alkylation might not proceed appreciably at such a low temperature. To test this we reverted to the methylation of **37**, which had previously worked extremely well, and studied the time course of this reaction. We found the reaction to be complete within 24 h and also determined that no regioisomeric products had formed (Table 4).[13] Moreover, we were extremely pleased to find that the diastereomer ratio for this reaction was >99:1.[15] An initial test of the scale-up of this reaction was conducted beginning with 4 g of **37** and proceeded without compromising the outcome of the transformation.[12]

Gratifyingly, we found that the use of these conditions with a range of hydrazones and alkylating agents gave the desired α,α-bisalkylated products in excellent yield, with *both* complete regio- and stereochemical control (Scheme 5).[16] The absolute configuration of the products was inferred by analogy to our previous experimental work[5] and recent theoretical studies.[6] An additional convenience of this bisalkylation procedure is that *either* enantiomeric ketone can be formed from the *same* auxiliary, following its cleavage, by simply changing the alkylation sequence. To highlight this, the alkylations in Scheme 5 were conducted in a pairwise fashion. In all cases, the α,α-bisalkylated product was formed with essentially complete regio-[13] and stereochemical control and in excellent yield, and the transformations were independent of the alkylation order.

To further probe the effectiveness of CIS-D, we next attempted the α,α-bisalkylation of hydrazone **54** (Scheme 6). The success of such a transformation would require that CIS-D be able to *completely reverse the normal preference of LDA* for removal of the significantly more acidic (∼6−7 pK_a units) benzylic (α′) protons of compound **54** during the first alkylation. This would also be true of the second alkylation. However, an additional challenge arises in this case, as there would no longer be a steric preference for α-deprotonation, since both the α and α′ acidic sites would now be methylene groups. To test the feasibility of this challenging sequence of transformations, compound **54** was prepared and then subjected to the first alkylation reaction using MeI as the electrophile. We were very pleased to find that only the α-product was formed[13] (**54** → **55**), thus indicating that CIS-D was indeed able to completely overcome the normal pK_a bias favoring α′ deprotonation. Even more impressively, the second allylation (**55** → **56**) also gave only α-alkylation,[13] and with excellent (>99:1)[15] diastereoselectivity. The α,α-bisalkylation was also conducted in the opposite sense with regard to the order of alkylation (**54** → **57** → **58**), and was equally effective. Significantly, in contrast to these results, it has been established that the SAMP hydrazone of ketone

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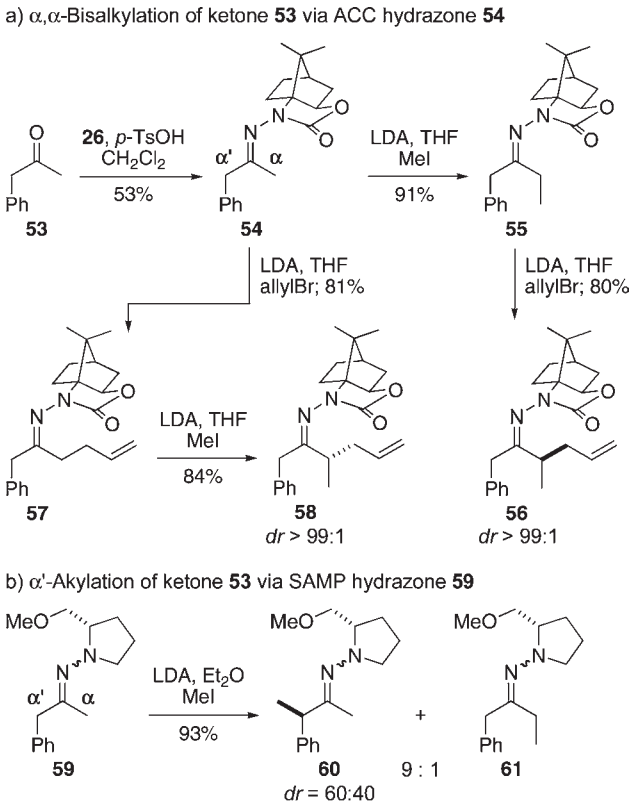
Scheme 6. (a) α,α-Bisalkylation via ACC Hydrazones and (b) α′-Alkylation via SAMP Hydrazones



Scheme 7. Formal Asymmetric Synthesis of (*R*)- and (*S*)-Stigmolone from a Common Intermediate

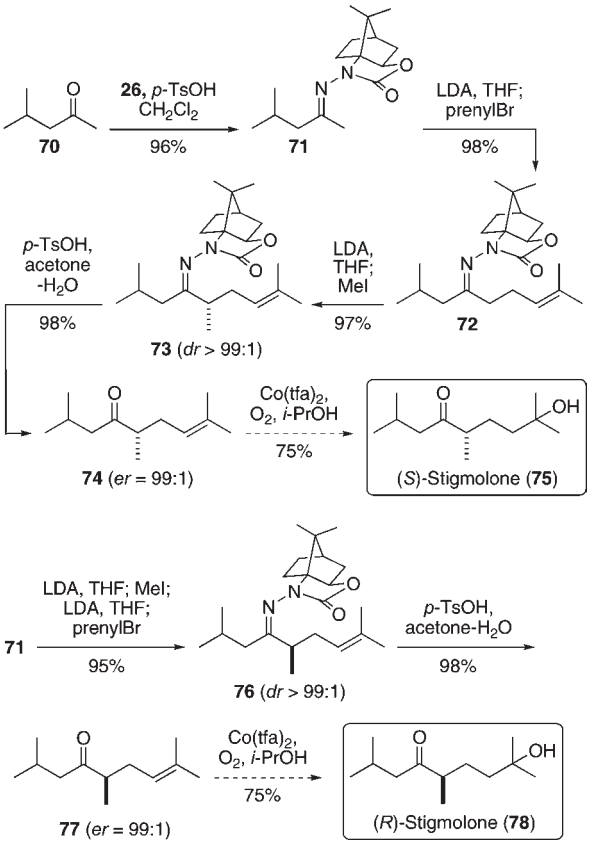
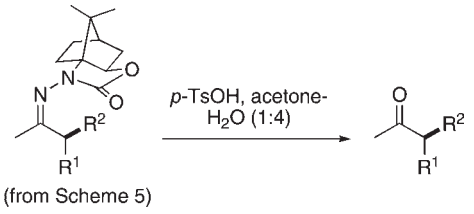


Table 5. Hydrolysis of Bisalkylated Hydrazones



entry	hydrazone (R^1; R^2)	hydrazone dr[a]	ketone	ketone er[a]	yield (%)
1	**45** (Me; Bn)	>99:1	**62**	>99:1	98
2	**46** (Bn; Me)	>99:1	**63**	>99:1	98
3	**47** (Et; allyl)	>99:1	**64**	n.d.[b]	95
4	**49** (allyl; Et)	>99:1	**65**	n.d.[b]	96
5	**50** (4-Br-$C_6H_4CH_2$; allyl)	>99:1	**66**	>99:1	98
6	**24** (allyl; 4-Br-$C_6H_4CH_2$)	>99:1	**67**	>99:1	97
7	**51** (4−-Br-$C_6H_4CH_2$; prenyl)	>99:1	**68**	>99:1	98
8	**52** (prenyl; 4-Br-$C_6H_4CH_2$)	>99:1	**69**	>99:1	98

[a] Determined by HPLC analysis. [b] Not determined.[17]

53 (i.e., **59**) undergoes alkylation preferentially at the α′-position (**59** → **60**), not the α-position, albeit with low diastereoselectivity. As such, the present method provides a convenient complementary strategy to the Enders method for the asymmetric alkylation of ketones possessing activating substituents.

At this point we turned our attention to the removal and recovery of the auxiliary from the bisalkylated products (Table 5). Thus, each of the α,α-bisalkyated hydrazones prepared in Scheme 5 was individually treated with *p*-TsOH·H_2O in acetone/H_2O, and in each case the desired ketone and **10** were obtained in excellent yield, the latter conveniently set for a second round of asymmetric α,α-bisalkylation. The er of the resulting ketones was determined via chiral HPLC, by reference to a mixture of enantiomers for which baseline separation conditions had been established. From these experiments it was determined that no epimerization occurred during auxiliary removal. Unfortunately, we were unable to effect baseline separation of compounds **64** and **65** utilizing the analytical equipment at our disposal. While we have no reason to expect that anything other than complete stereochemical integrity was maintained from this transformation, presently we cannot confirm this.

Finally, in order to demonstrate the utility of the above asymmetric α,α-bisalkylation method in a synthetic context, a formal asymmetric total synthesis of both (*R*)- and (*S*)-stigmolone was carried out utilizing the same ACC chiral auxiliary, **26** (Scheme 7).[18] Stigmolone is a highly potent pheromone secreted by the myxobacterium *Stigmatella aurantica*, which induces formation of fruiting bodies.[19] The synthesis of (+)-stigmolone began with the acid-catalyzed condensation of 4-methyl-2-pentanone and **26**, which provided ACC hydrazone **71** in 96% yield. This was then subjected to asymmetric α,α-bisalkylation by treatment with LDA and prenyl bromide, giving **72**, which then underwent LDA-mediated methylation to produce **73** in both excellent overall yield and diastereoselectivity (dr > 99:1).[15] Auxiliary

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cleavage proceeded efficiently to produce ketone **74** (er = 99:1).[20] Compound **74** has been shown to undergo cobalt-mediated oxidation to give (*S*)-stigmolone (**75**) in 75% yield, without epimerization occurring.[18c] Access to the ketone precursor needed for the preparation of (*R*)-stigmolone simply entailed switching the order of alkylation of hydrazone **71**, and also proceeded with excellent yield and diastereoselectivity (dr > 99:1).[15] Hydrolysis of bisalkylated product **76** produced ketone **77** (er = 99:1),[20] which has previously been converted to (*R*)-stigmolone (**78**) without epimerization occurring.[18c] Utilizing our α,α-bisalkylation method, ketones **74** and **77** were prepared from ketone **70** in overall yields of 89% and 87%, respectively, and with excellent enantioselectivity (er = 99:1). This compares favorably to a prior asymmetric synthesis of these ketones using the SAMP and RAMP auxiliaries.[18c] In that case, ketones **74** and **77** were generated from **70** in 27% and 14% overall yields, respectively, and with enantiomer ratios of 96.5:3.5 and 96:4, respectively.[21]

CONCLUSION

We have developed the first general method for the asymmetric α,α-bisalkylation of ketones having both α- and α′-protons, via CIS-D of ACC hydrazones. The transformation is efficient and proceeds with *both* excellent regio- and stereoselectivity. Significantly, CIS-D completely reverses the inherent preference of LDA to remove the least sterically hindered of two similarly acidic protons. It also overrides the normal tendency of LDA to remove the more strongly acidic proton in a substrate having protons differing significantly in their acidity. Consequently, the regiochemical outcome of this method is the opposite of that normally obtained for kinetic LDA-mediated deprotonation of ketones and SAMP/RAMP hydrazones. The method was successfully utilized for the concise and efficient asymmetric formal synthesis of both (*R*)- and (*S*)-stigmolone.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For an explanation of the stereochemical course of ACC alkylations, see refs 5 and 6.

(12) See the Supporting Information for details.

(13) Determined by ^{1}H NMR.

(14) Isomerization does occur if the hydrazone is exposed to acidic conditions.

(15) Determined by HPLC. See the Supporting Information for details.

(16) A third regioselective α-alkylation was attempted using **45** but resulted in the recovery of only nonepimerized starting material, suggesting that deprotonation had not occurred.

(17) Baseline resolution of the enantiomers could not be achieved using the equipment at our disposal. However, based on the other data in Table 5, we have no reason to suspect that the stereochemical integrity of **64** and **65** was compromised during hydrolysis.

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(21) The preparation of ketone **73** according to this method required HPLC purification of an advanced intermediate from dr = 92.5:7.5 to 99.5:0.5. See ref 18c.